Health Academy
Radboudumc

Examination	:	**B1RS1 Research Semester 1**
Date	:	January 27th, 2017
Start	:	13:00 h

After finishing the exam, you can take this examination set along with you.
Please hand in the OTHER part (the answering form) to the supervisor.

You are allowed to use a calculator of the type Casio FX-82MS.

The questions must be answered in English. If you cannot remember a specific English term, you are allowed to use the Dutch term.

During the exam you have access on a computer to these books:

- Baynes & Dominiczak: Medical Biochemistry
- van Oosterom en Oostendorp: Medische Fysica
- Campbell: Statistics at square one
- Fletcher: Clinical Epidemiology
- Turnpenny : Emery's Elements of Medical Genetics

GENERAL INSTRUCTIONS:

- This exam consists of **7** open questions.
- The available time is **2** hours.

- Check if your examination set is complete.
- Please write *your name and student number* on each page of the answering form.
- Write your answers on the answering form in the open space below the questions. Read the questions carefully before phrasing your answers.
- Be concise and complete in your answers.
- If necessary you can also use the *backside* of the pages.
- Refrain from using abbreviations in your answers, and write legibly (illegible answers are considered incorrect).
- Please do not use a pencil.
- The use of audiovisual and technical devices is not allowed, unless it is mentioned explicitly elsewhere on this page. Any inappropriate use of such equipment is regarded as fraud.
- Except for the exam forms, some loose writing material, your student and registration card your table should be empty. No boxes or cases are allowed.
- **After finishing the exam, please hand the answering form to the supervisor. If you have comments about the questions we refer you to the hyperlink of the digital comment form that is included in your "studenten webdossier" below "toetsen".**

SUCCESS!

ATTENTION !!

FIRST PUT YOUR NAME AND STUDENT NUMBER ON EVERY PAGE OF THE ANSWERING FORM!

1. Wet lab research: enzymes - Dr. G. Bosman

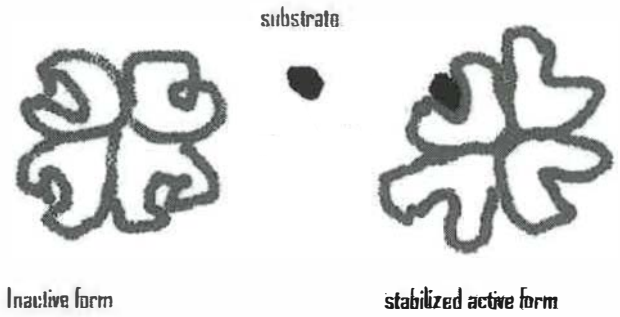
(10 points)

a) During the practical on enzyme kinetics you used a reaction mixture that, amongst others, contained hydrogenperoxide. The symbol above is displayed on the bottle that contains the hydrogenperoxide stock solution. Which class of compounds is labelled with this symbol? (1 pt)

b) The enzyme lactate dehydrogenase (LDH) catalyzes the reaction:

pyruvate + NADH → lactate + NAD^+

Suggest an experimental method for determining the rate of this reaction as catalyzed by LDH, that includes technical details. Also include your rationale. (3 pts)



c) The picture above shows an enzyme that consists of multiple subunits. Binding of a substrate at one subunit induces a conformational change in this subunit and consequently in the other subunits. In this way, part of the binding energy of the substrate is used to change the conformation of the whole protein complex, resulting in an increase in the affinity of the complex upon binding of substrate.

Draw the curve of reaction velocity versus substrate concentration for such an enzyme. (3 pts)

d) Indicate the Vmax and Km on the graph you generated in response to question 1c. (3 pts)

2. Modelling: Spread of an infectious disease - Dr. T. Oostendorp

(15 points)

In a simple model for the spread of an infectious disease people that are infected remain infective for the rest of their live. Consequently, in this model, people are either susceptible (that is: not yet infected) or infective. $I(t)$ denotes the number of infective people at time t.

If the number of infective people is relatively small, most people are susceptible, and the number of new infections per day is proportional to the number of infective people. In that case, the differential equation for the change in $I(t)$ is given by

$$\frac{d}{dt}I(t) = a\,I(t)$$

where a is the number of new infections per day caused by each infected individual.

a) Show that, according to the model, the number of infective people at time t is given by

$$I(t) = I_0 \mathrm{e}^{at}$$

with I_0 the number of infective people a $t = 0$t (4 pt).

b) Explain why this model cannot be correct for large values of t (3 pt).

For most infectious diseases, the patient is immune once he has recovered. Tuberculosis is an exception: after the patient has recovered, he is susceptible again. For tuberculosis, the above model can be extended to include recovery, which leads to this differential equation:

$$\frac{d}{dt}I(t) = a\,I(t) - r\,I(t)$$

where r is the fraction of infective people that recover per day.

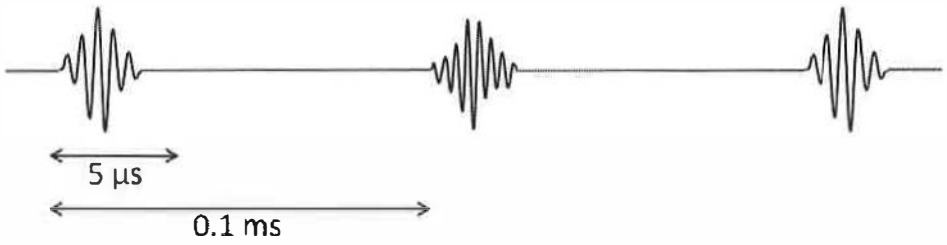
c) Show that this is the differential equation for the extended model (4 pt).

d) For what value(s) of $I(t)$ is, according to the extended model, the number of infected people constant (4 pt)?

3. Signals: Echoscopy - Dr. T. Oostendorp

(15 points)

In echoscopy an image is constructed by sending sound pulses into the body, and measuring the time it takes for the echo to arrive. This is converted in the distance to the structure that reflected the sound pulse.
A particular device emits pulses that have a duration of 5 μs. The frequency of subsequent pulse alternates between 1 MHz and 1.5 MHz. The interval between the pulses is 0.1 ms. The figure below is a sketch of the signal (not to scale).



The echo is converted into an electric signal, and subsequently sampled by a 10-bits AD-convertor with a range of 1 V.

a) What is the voltage resolution of the AD-convertor? Explain your answer (5 pt).

After AD-conversion the maximum sample value within an echo pulse is used to accurately determine the strength of the echo.

b) What is the minimum sample rate that should be used so that the maximum sample value represents the strength of the echo accurately? Explain your answer (5 pt).

c) Sketch the spectrum of the part of the signal that is depicted in the figure above. Indicate a few appropriate values along the x-axis (5 pt).

The following abstract and Tables belong to question 4, 5 and 6.

Maternal super-obesity and perinatal outcomes in Australia: a national population-based cohort study.

Sullivan et al. BMC Pregnancy and Childbirth (2015) 15:322
DOI 10.1186/s12884-015-0693-y

Abstract
Background: Super-obesity is associated with significantly elevated rates of obstetric complications, adverse perinatal outcomes and interventions. The purpose of this study was to determine the prevalence, risk factors, management and perinatal outcomes of super-obese women giving birth in Australia.
Methods: A national population-based cohort study. Super-obese pregnant women (body mass index (BMI) >50 kg/m2 or weight >140 kg) who gave birth between January 1 and October 31, 2010 and a comparison cohort were identified using the Australasian Maternity Outcomes Surveillance System (AMOSS). Outcomes included maternal and perinatal morbidity and mortality.
Results: 370 super-obese women with a median BMI of 52.8 kg/m2 (range 40.9–79.9 kg/m2) and prevalence of 2.1 per 1 000 women giving birth (95 % CI: 1.96–2.40). Super-obese women were significantly more likely to smoke (23.8 %) and be socio-economically disadvantaged (36.2 %). Compared with other women, super-obese women had a significantly higher risk for obstetric (adjusted odds ratio (AOR) 2.42, 95 % CI: 1.77–3.29) and medical (AOR: 2.89, 95 % CI: 2.64–4.11) complications during pregnancy, birth by caesarean section (51.6 %) and admission to special care (HDU/ICU) (6.2 %). The 372 babies born to 365 super-obese women with outcomes known had significantly higher rates of birthweight ≥4500 g (AOR 19.94, 95 % CI: 6.81–58.36).
Conclusions: Super-obesity in pregnancy in Australia is associated with increased rates of pregnancy and birth complications, and with social disadvantage. There is an urgent need to further address risk factors leading to super-obesity among pregnant women and for maternity services to better address pre-pregnancy and pregnancy care to reduce associated inequalities in perinatal outcomes.
Keywords: Super-obesity, Obesity, Perinatal outcomes, Pregnancy, Maternal socio-economic disadvantage, Obstetric complications.

Table 1 Demographic and obstetric characteristics among super-obese and comparison women who gave birth in Australia, 2010

	Super-obese group (*N* = 370)		Comparison (*N* = 621)		*P* value
	No.	%	No.	%	
Age (years)					
< 25	60	16.2	99	15.9	1.00
25–29	109	29.5	185	29.8	
30–34	110	29.7	187	30.1	
≥ 35	91	24.6	150	24.2	
Indigenous status					
No	341	92.2	572	92.1	0.23
Yes	17	4.6	19	3.1	
Not stated	12	3.2	30	4.8	
Marital status					
Single	71	19.2	71	11.4	<0.01
Married/cohabit	277	74.9	508	81.8	
Not stated	22	5.9	42	6.8	
Private health insurance					
No	356	96.2	474	76.3	<0.01
Yes	14	3.8	145	23.3	
Not stated	0	0.0	2	0.3	
Smoking during pregnancy					
No	265	71.6	484	77.9	<0.01
Yes	88	23.8	100	16.1	
Not stated	17	4.6	37	6.0	
Assisted reproductive technology					
No	357	96.5	574	92.4	0.17
Yes	11	3.0	29	4.7	
Not stated	2	0.5	18	2.9	

Indigenous status means 'native', 'autochthonous'

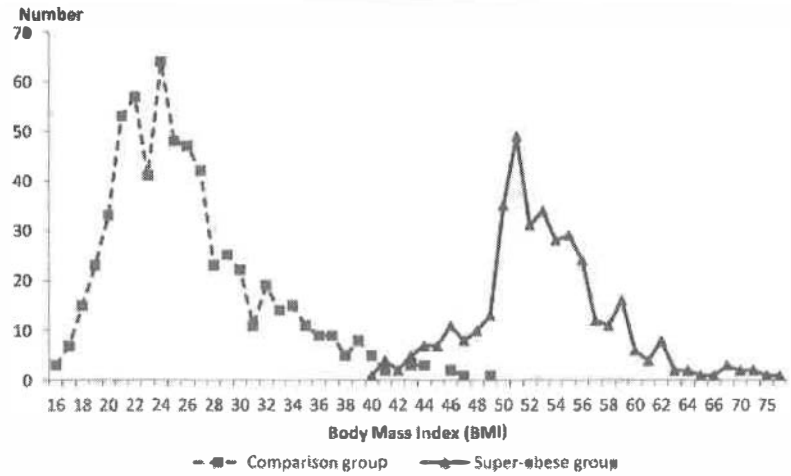


Fig. 2 Distribution of body mass index of super-obese and comparison women who gave birth in Australia, 2010

Table 2 Model of care among super-obese and comparison women who gave birth in Australia, 2010

	Super-obese group ($N = 370$)		Comparison ($N = 621$)		*P* value
	No.	%	No.	%	
Lead care provider					
General practitioner	72	19.5	122	19.6	<0.01
Hospital medical	247	66.8	175	28.2	
Hospital midwife	34	9.2	182	29.3	
Private obstetrician	17	4.6	140	22.5	
Not stated	0	0.0	2	0.3	
Changed during pregnancy					
No	312	84.3	566	91.1	<0.01
Yes	56	15.1	55	8.9	
Not stated	2	0.5	0	0.0	
Transfer					
No	326	88.1	596	96.0	<0.01
Yes	44	11.9	25	4.0	
Timing of maternal transfer					
Antepartum	34	77.3	19	76.0	0.77
Intrapartum/Postpartum	9	20.5	6	24.0	
Not stated	1	2.3	1	0.0	

Table 3 Labour and birth characteristics among super-obese and comparison women who gave birth in Australia, 2010

	Super-obese group ($N = 370$)		Comparison ($N = 621$)		*P* value
	No.	%	No.	%	
Multiple births					
Singleton	362	97.8	608	97.9	0.81
Twin	8	2.2	12	1.9	
Not stated	0	0.0	1	0.2	
Labour					
No	125	33.8	139	22.4	<0.01
Yes	241	65.1	482	77.6	
Not stated	4	1.1	0	0.0	
Induction of labour					
No	100	41.5	351	72.8	<0.01
Yes	140	58.1	129	26.8	
Not stated	1	0.4	2	0.4	
Method of birth					
Vaginal birth	176	47.6	424	68.3	<0.01
Caesarean section	191	51.6	197	31.7	
Not stated	3	0.8	0	0.0	
Caesarean section					
Planned	103	53.9	122	61.9	0.1
Unplanned	87	45.5	73	37.1	
Not stated	1	0.5	2	1.0	
Use of general anaesthetic					
No	172	90.1	191	97.0	0.01
Yes	19	9.9	6	3.0	

4. Population Research: Methods and measures in human based research – Dr. F. de Vegt (10 points)

a) How was 'super-obesity' defined in this study? (2 pnt)

b) Which two variables are needed and were measured to calculate the variable 'super-obesity'? (2 pnt)

c) List two other ways to obtain information about obesity from humans, define the measure for obesity that you will obtain with these, and mention one advantage and one disadvantage for each measurement method. (4 pnt)

d) See the results section of the abstract. Give an interpretation for the result: '370 super-obese women with a median BMI of 52.8 kg/m2 (range 40.9–79.9 kg/m2) and prevalence of 2.1 per 1 000 women giving birth (95 % CI: 1.96–2.40)' (2 pnt)

5. Population Research: Etiological research on pregnancy outcomes – Dr. N. Roeleveld (15 points)

Please look back at the fragments of the paper presented before Question 4.

a) The abstract states that this was a population-based cohort study. But was it a prospective or a retrospective cohort study? Please explain. (2 points)

b) Which are the determinant(s) and the outcome(s) in this study? (2 points)
super obese adverse perinatale

c) Assuming that the comparison group is a good representation of the general population of women giving birth in Australia, what is the interpretation of the results seen in Table 1? (3 points)
welke variabelen gelden voor wie

d) Would the differences seen in Table 1 lead to selection bias or confounding of the results, if you would not take them into account in the analyses? (2 points)
yes single health insurance.

e) Look at 'Method of birth' in Table 3. Now calculate two different measures of association for having a caesarean section. Ignore the 3 women for whom method of birth was not stated (so the super-obese group contains 367 women for this variable). Please show your calculation, not only the end-result. (4 points)

$\frac{a/b}{c/d}$ $\frac{191/176}{197/424} = 2,3$

f) Assuming that the measures of association calculated in question 5e are above 1 with 95% CIs excluding 1, how would you interpret both of these results (use words such as 'risk' and/or 'association'). (2 points)

association between CS and obese

6 **Statistics – Dr. R. Donders**
(15 points)

Please look back at the fragments of the paper presented before Question 4.

a) As measure for the location of the weight of the super-obese women, the authors chose to use the median. Give a reason why the authors preferred the median over the more common mean as measure for location (4 points).

outliers (fig 2)

b) From Table 2 you can read that 11.9% of the super-obese women were transferred. What would be your estimate for the standard error for this percentage? (4 points)

c) Show that there is at least one super-obese woman with a length greater than 1.85 m. Hint: look at the inclusion criteria and the range of the BMI scores and remember that BMI is defined as weight in kg/(length in m)^2. (4 points)

kg = 171

d) What is the median BMI in the comparison group? Give the median in a round number (no fractions or decimals). (3 points)

25

~~7~~ **Wet lab research - Genetic Lab practice – Dr. D. de Bruin**
(15 points)

a) Besides water and genomic DNA, the Polymerase Chain Reaction (PCR) mix contains several other essential components. Name two of these components and give a short explanation how they contribute to DNA amplification. (4 pt)

P DNA-pol
nucleotide

b) Below you see a list of five different types of genetic variation in alphabetic order. Reorder these according to which can be measured <u>best</u> with Sanger sequencing. Start with the variant type that can be measured best. (3 pt)

A. Copy number variation (CNV)
B. Insertion-deletion (indel)
C. Repeat length variation
D. Single nucleotide variation (SNV)
E. Translocation

B D C A E

Below, you see a snapshot from the 1000Genomes browser with genotype information of SNP rs12913832. This table contains genotype frequencies and numbers of persons per genotype (between brackets) for four different European populations (i.e. CEU=Northern and Western European ancestry, FIN=Finnish, GBR=British, IBS=Spanish).

1000GENOMES phase_3: **CEU**	**A|A**: 0.040 (4)	**A|G**: 0.384 (38)	**G|G**: 0.576 (57)
1000GENOMES phase_3: **FIN**	**A|A**: 0.000 (0)	**A|G**: 0.182 (18)	**G|G**: 0.818 (81)
1000GENOMES phase_3: **GBR**	**A|A**: 0.044 (4)	**A|G**: 0.275 (25)	**G|G**: 0.681 (62)
1000GENOMES phase_3: **IBS**	**A|A**: 0.449 (48)	**A|G**: 0.458 (49)	**G|G**: 0.093 (10)

c) Calculate the *allele frequency* of the A and G alleles for the CEU population. Write down your calculations and round your results to 3 decimals. (3 pt)

	A	G
Allele frequency CEU	0,232	0,768

d) Use the A and G allele frequencies from 7c to calculate the expected *genotype frequencies* (AA, AG and GG) for the CEU population under assumption of Hardy-Weinberg Equilibrium. Write down your calculations and round your results to 3 decimals. (2 pt)

	AA	AG	GG
Genotype frequency CEU	0,053	0,354	0,593

e) Use the genotype frequencies from 7d to calculate the expected *number of persons* for each genotype in the CEU population (total number of persons comes from the 1000genomes table). Write down your calculations and round your results to whole numbers. (1 pt)

	AA	AG	GG
Number of persons CEU	5	35	59

f) Compare the actual numbers of person for each genotype in the CEU population from the 1000genomes table with the expected number of genotypes that you calculated in 7e. What is your evaluation of the differences between these genotype distributions? (2 pt)

	AA	AG	GG
Actual (100genomes)	4	38	57
Calculated (answer 7e)	5	35	59